Recommendations to Support Deprescribing Medications Late in Life

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The problems associated with medication use have long been recognized, including the impact of adverse drug events, the consequences of inappropriate medication use, and the burden of taking multiple medications as part of a complex, costly regimen. General solutions to these challenges have seen the development of various standards, such as the Beer's Criteria [1], and STOPP/START (screening tool of older people's prescriptions/screening tool to alert to right treatment) criteria [2], to support prescribers in their decision-making. These standards involve the identification and reduction of various medication-related problems, including inappropriate medication use and potential drug-drug interactions. Many studies have, to date, demonstrated the utility of these standards when applied to an elderly population, and have focused around reducing inappropriate medication amongst this group [3].

Despite this success, it would appear that the utility of these standards is not directly transferable to all populations: improving the prescribing for patients with severe illness, advanced age, multi-morbidity, and diminishing life expectancy requires a different approach. For example, if we consider statin therapy for primary or secondary prevention of cardiovascular disease: several cohort studies have shown that statin therapy is inappropriate among patients with advanced illness and subsequent diminished life expectancy [4,5]. Indeed, a recent controlled trial by Kutner and colleagues [6], who discontinued statin therapy in patients with an estimated life expectancy of between 1 month and 1 year, showed there was no significant difference in terms of mortality within 60 days of statin discontinuation compared to participants who continued their statins, suggesting it is safe to stop statins in the context of advanced illness. Perhaps more significantly, however, in the same trial, patients who had their statin therapy discontinued appeared to have a significantly better quality of life. If we consider this scenario using the Beer's Criteria and STOPP/START criteria to support decision-making and assess medication appropriateness, statin therapy in this context would be considered 'appropriate'. Indeed, many preventive medications are considered appropriate and recommended for healthy older patients, but are considered inappropriate, or even 'futile' at the end of life [7].

This dichotomy illustrates the challenges for prescribing medication for patients with diminished life expectancy, in which a 'shift' necessarily occurs in the medications that are rational and appropriate for an individual patient. Predicting the timing of this shift and effectively discontinuing inappropriate medication for patients with diminished life expectancy is challenging – especially considering there is no clear guidance for those who make prescribing decisions.

As a result of these challenges, several conceptual frameworks – used to prioritize medications late in life – have been developed [8-10]. These frameworks, although highly conceptual, consider the remaining life expectancy of the patient, and other factors, such as goals of care and time until benefit and offer a different approach to the conventional standards. Indeed, several studies have used these frameworks and have demonstrated that many patients in end-of-life care continue to take medication that is no longer appropriate [7, 11-12]. At present, however, despite this evidence, there are still no incentives – or supportive guidance – to use or apply these conceptual frameworks in clinical practice. This problem will continue until policy-makers feel compelled to prioritize medications late in life and offer appropriate guidance to healthcare professionals involved in medication use.

Now is the time to address this problem. Prescribing will only become more challenging due to the aging population, the burden of multi-morbidity, and restricted resources. As the global population ages and more people present with multiple chronic conditions, applying more and more therapies on top of pre-existing ones is not only not practical, it is burdensome and, in some cases harmful. Furthermore, financial toxicity is increasingly recognized as an adverse consequence of treatment [13]. Even more challenging is the increasing number of guidelines focused on the initiation of medications, particularly those aimed at prevention. For example, newer cholesterol guidelines in the United States recommend the initiation of statins for patients with lower cardiovascular risk than previously recommended, resulting in a projected increase from 38% to 87% in persons eligible for therapy [14]. Similarly, in the UK, NICE

guidelines will incorporate a recommendation to start statin once a patient's 10-year cardiovascular risk is estimated at 10% or greater, resulting in many more patients eligible for therapy.

Even the guidelines for end-of-life care are focused on treating symptoms with more medication, rather than less [15]. However, healthcare providers who care for patients at the end of life are faced with real challenges in rationalizing medication use. Another reason for the urgent need for guidance is the mandate to better streamline care at the end of life, such as the effort to consolidate the Medicare hospice and Part D prescription drug benefits [16-17]. It is apparent that the trend toward increasing medication use in later life cannot continue.

Rather than adding more guidelines that advocate initiating more care, guidelines should directly address the appropriate removal of therapy. When looking for a model for such decisions, we turned to the challenges in using cardiac devices while planning for appropriate end-of-life care. We would argue that the principles of prescribing medication and using an implantable cardiac device are the same: the benefits must be continually balanced and assessed against the risks. However, in the case of implantable cardiac devices, there is clear recognition that clinicians need guidance to explain how and when therapy should be stopped. We, therefore, argue that rational prescribing and medication discontinuation in diminished life expectancy should be viewed through the same lens as the use of implantable cardiac devices in advanced heart failure [18].

In this commentary we present five recommendations for rationalizing medication use, and propose that rationalizing medication use late in life should be incorporated into guidelines and considered an imperative for all healthcare providers – not just those that work in a specialist palliative care environment. As the broader literature shows many patients are prescribed statins inappropriately late in life, and the recent trial by Kutner and colleagues [6], illustrating that statin discontinuation in patients with advanced illness resulted in an improved quality of life without impacting on survival, we discuss each recommendation in the view of statin therapy.

1) *Shared decision-making is also about prescribing medications.* Prescribers have an ethical responsibility to involve patients in decision-making about medication use. During a consultation about initiating a medication, healthcare professionals should be able to take the time required to have open discussions with patients about benefits and harms so that they can decide together whether a medication is a good option [19]. In the case of statins, the widespread use, promoted by new guidelines, means that many more people unlikely to benefit from statins will receive them. Discussing the decision to use a statin is important in this context. Ultimately, the prescribing of medications that are largely preventive based on such guidelines without shared decision-making is inherently paternalistic.
2) *Not prescribing a medication should be presented as a reasonable alternative for patients late in life, when appropriate.* Patients have the right to choose therapy from reasonable options. Particularly in patients with limited life expectancy, the choice to not prescribe a medication, especially a preventive medication, is often a reasonable alternative. This point illustrates the fact that for patients late in life, with advanced age, advanced illness, or multi-morbidity, many decisions will be preference-sensitive. Situations in which the risk-benefit ratio for different treatment options is unclear, a patient's values, goals, and preferences should be prioritized to frame a prescribing decision.[16] In the case of a statin, there is a lack of evidence for substantial benefit for many subgroups of patients of advanced age or with multi-morbidity [20]. In this context, not prescribing a statin to a patient with diminished life expectancy is a reasonable choice given the current evidence base.
3) *Deprescribing is part of prescribing.* Medications are burdensome interventions and, therefore, prescribing medications should always include a consideration of how long a therapy will be continued and when and how it should be discontinued. Statin use should be accompanied by a consideration of when it would be no longer beneficial to a patient or when it could become burdensome. A statin could be stopped when the time to benefit – defined as the time for a

population to realize the intended effect of the medication – is longer than a patient's estimated remaining life expectancy; this consideration should occur at the point of initial prescribing.

4) *Prescribers have to embrace uncertainty.* Prescribing involves estimation of benefits and harms, prognosis, and competing risks, and extrapolation of evidence to an individual clinical situation, all of which are inherently uncertain. Reducing medication use should not be delayed until a poor prognosis is certain, such as when patients are referred to a palliative care team for specialist end of life care. Rather, when treating patients with diminishing life expectancy, clinicians should be more willing to embrace the uncertainty of stopping medications. In the case of statins, for example, prescribers will necessarily be unsure about stopping a statin, without being able to know a patient's precise prognosis and cardiovascular risk. The uncertainty inherent in prescribing medications must be acknowledged and overcome.

5) *"Difficult discussions now will simplify difficult decisions in the future."*[18] This statement on cardiac devices in advanced heart failure captures the pertinence of this proposed approach when applied to prescribing. When a medication is started, a discussion about when, why, and how to stop it should be initiated with the patient. There should be a discussion about a patient's current status and likely disease trajectory, and how the medication fits into a treatment plan given this anticipated trajectory and possible changes in goals of care. When starting a preventive therapy like a statin, initiation of the medication should be framed in terms of overall health and disease risk. A plan should be in place for when the statin is no longer part of the overall care plan. When patients ask how long statins will be taken and clinicians respond, "*for the rest of your life*," patients literally take this to mean that they will never stop the statin until the day they die. This creates difficult decisions later for healthcare professionals providing end-of-life care, who are left explaining why patients should stop their statins. The time commitment involved in these initial discussions means that they may get deferred or never even happen. In the context of other complex decisions, prescribing a preventative medication is easiest without a lengthy discussion.

We articulate these five recommendations to illustrate that every healthcare professional has a role in the rationalizing of medications for patients late in life. The obligation to address appropriate medication use is not merely on the original prescriber; it is every prescriber's responsibility to provide care that is consistent with patients' goals, values, and preferences.

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